

## **REMARKS/ARGUMENTS**

### **Status of the Claims**

Claims 1, 3-77, 138, and 139 are under examination and are rejected. Claims 2 and 78-137 were previously canceled and claims 71 and 73-74 are canceled by this amendment. Claims 1, 4, 6, 12, 14, 19-20, 22-24, 26, 41, 46, 48-49, 51-52, 56, 65, 68-70, 72, 75-77, and 138 are amended. New claims 140-142 are added. Claims 1, 3-70, 72, 75-77, 138-139, and 140-142 are pending.

### **Claim Amendments**

Claims 71 and 73-74 are canceled and have been rewritten in independent form to include the elements of claim 69 from which they depend as new claims 140-142, respectively.

Claims 1, 4, 6, 12, 14, 19-20, 22-24, 26, 41, 46, 48-49, 51-52, 65, 68-70, 72, 75-77, and 138 are amended to consistently recite "carrier-mediated transport protein" throughout.

The preamble of claim 1 is amended to recite "a" rather than "the" cell surface to establish proper antecedent basis. Claim 1, step (b) is amended to recite ", each cell having a surface comprising a plasma membrane" to establish proper antecedent basis for "the plasma membrane of the cell surface" as recited throughout the claims. In view of this amendment, step (b) is further amended by replacing the phrase "which expresses" with "the cells expressing" to more clearly state the presently claimed invention.

Claims 4, 6, 12, 19, 20, and 22 is amended to depend from independent claim 1, in view of the previously canceled claim 2.

Claim 56 is amended by deleting the term "test" more clearly to state the presently claimed invention.

Claims 69, 75, and 76 are amended by adding step "(a) providing a library comprising different complexes, each complex comprising a compound and a separate reporter, the compound varying between different complexes." Support for providing a library of complexes can be found, for example, on page 22, lines 2-20 of the as-filed application. Claims 69, 75, and 76 are also amended to recite that the one or more cells are simultaneously contacted with a

plurality of complexes from the library. Support for this amendment can be found, for example, on page 14 of the as-filed specification, which discloses multiplexed methods that provide for simultaneously screening multiple different complexes on the same cells.

Claim 69 is also amended to recite “that if the reporter comprises a fluorophore, the complex comprises a compound, a fluorophore and a quencher, and the fluorophore is linked to the quencher by a linker susceptible to cleavage within the cell, whereby the quencher quenches fluorescence from the fluorophore outside the cell and is cleaved from the fluorophore within the cell after the complex is internalized within the cell, whereby the reporter preferentially generates the signal once internalized within the cell.” Support for a complex comprising a compound, a fluorophore, and a quencher can be found, for example, on page 34, line 13 to page 35, line 25 of the as-filed application.

Thus, the amendments to the claims are fully supported by the specification as originally filed and add no new matter.

### **Interview Summary**

Applicants accept the Examiner's interview summary of the interview conducted October 12, 2006.

### **Objections to the Claims**

**3.A.** Claim 64 is objected to under 37 C.F.R. § 1.75(c) as being of improper dependent claim form for failing to further limit the subject matter of a previous claim. The Examiner alleges that “combinatorial library” does not limit the subject matter of claim 1. Applicants respectfully traverse.

Claim 1 recites a “library comprising different complexes.” Each complex in the library comprises a compound and a separate reporter, and the compound varies between different complexes. On page 22, lines 16-20 of the originally filed specification, Applicants disclose that the compound in the “complexes can be from random libraries, combinatorial libraries, libraries of variants of a known substrate, [sic] natural product libraries.” Therefore, the source of the compounds used in the library comprising different complexes can themselves be from among different libraries, one of which is a combinatorial library. A combinatorial library is one formed

by combining building blocks to form the compounds of the library. Furthermore, combinatorial library modifies the compound in claim 1, step (b), and not the “library comprising different complexes.” Accordingly, claim 64 appropriately limits the subject matter of claim 1 from which it depends and therefore satisfies the requirements of 37 C.F.R. § 1.75(c).

In view of the foregoing, Applicants respectfully request withdrawal of the objection of claim 64 under 37 C.F.R. § 1.75(c) as being of improper dependent form.

**Claim Rejections – 35 U.S.C. § 112, second paragraph**

**4.A.** The Examiner rejects claims 1, 69, and 75-77, and all dependent claims, under 35 U.S.C. § 112, second paragraph as being vague and indefinite in the use of the word “type” in the phrase “carrier-type. The Examiner recommends that the phrase “carrier-mediated” be used.

Applicants have amended claims 1, 69, and 75-77 by replacing the phrase “carrier-type” with “carrier-mediated” thereby addressing the Examiner’s rejection.

**4.B.** The Examiner rejects claim 1 and all dependent claims for lacking antecedent basis for the element “the plasma membrane of the cell surface.”

Applicants have amended claim 1, step (b) to recite that each cell has a surface comprising a cell membrane, thereby establishing an antecedent basis for subsequent recitations of “the plasma membrane of the cell surface” thereby addressing the Examiner’s rejection.

**4.C.** The Examiner rejects claim 14 and all dependent claims under 35 U.S.C. § 112, second paragraph, for insufficient antecedent basis for the element “the plasma membrane of the cell surface.” This phrase is not recited in claim 14 or in any other claim other than claim 1. Therefore, Applicants believe that this rejection is in error.

**4.D.** The Examiner rejects claim 56 and all dependent claims under 35 U.S.C. § 112, second paragraph for insufficient basis for “the test compound.”

Applicants have amended claim 56 by deleting the word “test” thereby addressing the Examiner’s rejection.

**4.E.** The Examiner rejects claims 4, 6, 12, 19, 20, and 22, and all dependent claims, under 35 U.S.C. § 112 for failing to particularly point out and distinctly claim the subject matter because the claims depend on a canceled claim.

Applicants have amended claims 4, 6, 12, 19, 20, and 22 to correct the claim dependency thereby addressing the Examiner's rejection.

**4.F.** The Examiner rejects claims 4, 12, 14, and 72 under 35 U.S.C. § 112, second paragraph for insufficient antecedent basis for the claim element "carrier type protein."

Applicants have amended the claims to consistently recite "carrier-mediated transport protein" throughout, thereby addressing the Examiner's rejection of claims 4, 12, 14, and 72.

**4.G.** The Examiner rejects claims 6 and 70 under 35 U.S.C. § 112, second paragraph for insufficient antecedent basis for "carrier type transporter protein."

Applicants have amended the claims to consistently recite "carrier-mediated transport protein" throughout, thereby addressing the Examiner's rejection of claims 6 and 70.

In view of the foregoing, Applicants respectfully request withdrawal of the rejections of claims 1, 3-77, 138, and 139 under 35 U.S.C. § 112, second paragraph.

### **Claim Rejections – 35 U.S.C. § 102**

An anticipatory reference under 35 U.S.C. § 102 must disclose each limitation of the claims (*M.P.E.P.* § 2131, Rev. 5. August 2006, p. 2100-67; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.")).

**5.** The Examiner rejects claim 69 under 35 U.S.C. § 102(b) as anticipated by Homolya *et al.* (Homolya *et al.*, *J. Biol. Chem.* 1993, 368(29), 21493-21496). The Examiner

alleges that Homolya *et al.* disclose: (a) providing one or more cells that express a carrier-type transport protein; (b) contacting the one or more cells with one or more complexes, each complex comprising a compound and a reporter; and (c) selectively detecting a signal from a reporter internalized within one or more cells as compared to signal from a reporter outside the cell. Applicants respectfully traverse the rejection of claim 69 over Homolya *et al.*

Homolya *et al.* describe the uptake of fluorescent dyes into NIH-3T3 fibroblasts expressing the human multidrug transporter (MDR1). Fibroblasts that express the human multidrug transporter were found to actively extrude the hydroxy acetoxymethyl ester (AM) derivatives of various fluorescent calcium and pH indicators but not the free acid forms of the fluorescent indicators (Abstract and page 21493).

Applicants have amended claim 69 to recite that when the reporter comprises a fluorophore, the complex comprises a compound, a fluorophore, and a quencher. As acknowledged by the Examiner, Homolya *et al.* do not disclose a compound/fluorophore/quencher structure. Therefore, Homolya *et al.* do not disclose each element recited in claim 69, and therefore Homolya *et al.* cannot anticipate claim 69.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claim 69 under 35 U.S.C. § 102(b) as anticipated by Homolya *et al.*

6. The Examiner rejects claims 69 and dependent claims 70 and 72 under 35 U.S.C. § 102(b) as being anticipated by Swanson *et al.* (Swanson *et al.*, *The Plant Cell* 1998, 10, 685-698) as evidenced by Ozkan *et al.*, *Biochim Biophys Acta* 2002, 1572, 143-148). The Examiner alleges that Swanson *et al.* disclose: (a) use of a library of fluorescent conjugates comprising (a) providing one or more cells expressing a carrier-type transport protein; (b) contacting the one or more cells with one or more complex, each complex comprising a compound a reporter; and (c) detecting a signal fro a reporter internalized within the one or more of the cells as compared to signal form reporter outside the cell. Applicants respectfully traverse.

Applicants have amended independent claim 69 to include additional step (a), which recites “providing a library comprising different complexes, each complex comprising a compound and a separate reporter, the compound varying between different complexes;” and

amending step (c) (original step (b)) to recite contacting the cells with a plurality of complexes from the library simultaneously.

Swanson *et al.* do not disclose or suggest the step of “providing a library comprising different complexes.” All of the reporters disclosed by Swanson *et al.* are fluorophores. As recited in claim 69, a complex comprising a fluorophore further comprises a compound and a quencher. BCECF-AM and ZFR-GMAC are not complexes as claimed because BCECF-AM and ZFR-GMAC are reporter/quencher complexes, which lack the claimed compound element. Assuming *arguendo* that ZFR-CMAC-GS does fit the claimed complex, it is the only complex disclosed by Swanson *et al.* Therefore, Swanson *et al.* disclose at most one complex, and not a “library comprising different complexes.” Swanson *et al.* also do not disclose the “simultaneous” screening of complexes as recited in amended claim 69. The complexes disclosed by Swanson *et al.* are tested separately on the cells. Because Swanson *et al.* do not disclose each element recited in claim 69, Swanson *et al.* cannot anticipate the claim.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claim 69 and claims 70 and 72, which depend therefrom, under 35 U.S.C. § 102(b) as anticipated by Swanson *et al.*

The Examiner rejects claim 75 under 35 U.S.C. § 102(b) as being anticipated by Swanson *et al.* as evidenced by Ozkan *et al.* The Examiner alleges that Swanson *et al.* disclose (a) providing a plurality of different cells located in a single reaction vessel with each cell expressing a carrier type transport protein and different cells having different distinguishable characteristics; (b) contacting the plurality of different cells with one or more complexes with each complex comprising a compound and a reporter whereby at least one complex is bound to or internalized within one of the cells; (c) detecting a signal from the reporter of the at least one complex bound to or internalized within the cell; and (d) determining the identity of the cell from its distinguishable characteristic. Applicants respectfully traverse.

Applicants have amended independent claim 75 to include additional step (a), which recites “providing a library comprising different complexes, each complex comprising a compound and a separate reporter, the compound varying between different complexes,” and

amended step (c) (original step (b)) to recite contacting the cells with a plurality of complexes from the library simultaneously. As set forth for claim 69, Swanson *et al.* do not disclose a library of complexes, and do not disclose contacting the cells with a plurality of complexes from the library simultaneously. Because Swanson *et al.* do not disclose each element recited in Applicants' claim 75, Swanson *et al.* cannot anticipate the claim.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claim 75 under 35 U.S.C. § 102(b) as anticipated by Swanson *et al.*

The Examiner rejects claim 76 under 35 U.S.C. § 102(b) as being anticipated by Swanson *et al.* as evidenced by Ozkan *et al.* The Examiner alleges that Swanson *et al.* disclose (a) providing one or more cells with each cell expressing a carrier-type transport protein and located in a single reaction vessel; (b) contacting the one or more cells with a plurality of different complexes with each complex comprising a compound and a reporter, the compound and reporter varying between different complexes and different reporters disposed to generate different signals whereby at least one complex is bound to or internalized within the one or more cells; and (c) detecting the signal from the reporter of the at least one complex the signal providing an indication of the identity of the compound borne by the at least one complex. Applicants respectfully traverse.

Applicants have amended independent claim 76 to include additional step (a), which recites "providing a library comprising different complexes, each complex comprising a compound and a separate reporter, the compound varying between different complexes;" and amending step (c) (original step (b)) to recite contacting the cells with a plurality of complexes from the library simultaneously. As set forth for claim 69, Swanson *et al.* do not disclose a library of complexes, and do not disclose contacting the cells with a plurality of complexes from the library simultaneously. Because Swanson *et al.* do not disclose each element recited in claim 76, Swanson *et al.* cannot anticipate the claim.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claim 76 under 35 U.S.C. § 102(b) as anticipated by Swanson *et al.*

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**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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